

REMARKS

Claims 1-3, 7, 8, 12, 16 and 17 are pending. Favorable reconsideration is respectfully requested.

The present invention relates to a method for the treatment of brain edema, comprising administering an effective amount of a composition comprising melatonin to a subject having brain edema. See Claim 1.

The rejection of the claims under 35 U.S.C. §103(a) over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) is respectfully traversed.

Thomas discloses that heat or H<sub>2</sub>O<sub>2</sub> inactivation of superoxide dismutase (SOD), an antioxidant which partially blocks (Fig. 3) vasoconstriction induced by beta-amyloid (Fig. 10), results in partial reduction of the relaxing activity possessed by the SOD on the constriction (Fig. 12). However, Thomas does not disclose anything about a correlation between SOD and any brain disease. With the experimental data provided by Thomas, it cannot be concluded that an antioxidant cures any brain disease. In fact, Thomas has failed to demonstrate that SOD or other antioxidants can cure even Alzheimer's disease, which specifically results in accumulation of beta-amyloid.

Hiraide discloses the reduction of cerebral water content with a specific beta-hydroxybutylate derivative. However, this reference does not disclose anywhere with experimental data that the reduction is caused by scavenging free radicals generated due to ischemia or cellular injury.

Nishino discloses that particular compounds having anti-oxidation activity reduce brain moisture content in the data from column 12, line 65 to column 16, line 41. However, the data do not demonstrate that the moisture reduction is caused by the anti-oxidation activity (determined by Radical Eliminating Effect Test (DPPH), column 10, lines 62-67) of

the compounds, since most of the compounds having the DPPH reducing effect do not reduce the brain moisture (see Tables 1 and 2). Thus, Nishino demonstrates with experimental data that anti-oxidative activity cannot be correlated even with reduction of brain moisture.

Chein discloses a hormone replacement therapy. See the Abstract. The Examiner has cited column 4, lines 18-27 for the proposition that melatonin is a free-radical scavenger. See the Official Action dated March 28, 2005, at page 3.

The combination of Thomas, Hiraide, Nishino, individually or in combination, in further combination with Chein, fails to suggest the claimed method. Nishino demonstrates with experimental data that anti-oxidative activity cannot be correlated even with reduction of brain moisture. For that reason, there is no motivation provided by the cited references to use melatonin to treat brain edema. Therefore, the claimed method is not obvious over those references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record is respectfully traversed.

Nishino demonstrates with experimental data that anti-oxidative activity cannot be correlated even with reduction of brain moisture, as discussed above. For that reason, there is no motivation provided by the cited references to use melatonin to treat brain edema. Therefore, the claimed method is not obvious over the cited references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) or over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record as set forth in view of Keller (5,891,465) is respectfully traversed.

Nishino demonstrates with experimental data that anti-oxidative activity cannot be correlated even with reduction of brain moisture, as discussed above. For that reason, there is no motivation provided by the cited references to use melatonin to treat brain edema. Therefore, the claimed method is not obvious over the cited references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Thomas (6,011,019), Hiraide (6,136,862), Nishino (5,849,930) individually or in combination, in further combination with Chein (5,855,920) as set forth above, further in view of WO 97/20555 of record as set forth above, further in view of Wurtman (4,687,763) of record is respectfully traversed.

Nishino demonstrates with experimental data that anti-oxidative activity cannot be correlated even with reduction of brain moisture, as discussed above. For that reason, there is no motivation provided by the cited references to use melatonin to treat brain edema. Therefore, the claimed method is not obvious over the cited references. Withdrawal of this ground of rejection is respectfully requested.

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Reply to Office Action of March 28, 2005

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

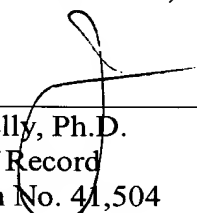
Respectfully submitted,

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